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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/546,139	07/19/2006	Michel Chateau	34076/US/2	1181

25763 7590 11/24/2008

DORSEY & WHITNEY LLP
INTELLECTUAL PROPERTY DEPARTMENT
SUITE 1500
50 SOUTH SIXTH STREET
MINNEAPOLIS, MN 55402-1498

EXAMINER	
LONG, SCOTT	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
11/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/546,139	CHATEAU ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/28/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14 and 38-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,14 and 38-49* is/are rejected.

7)☒ Claim(s) *49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/25/2008 has been entered.

Claim Status

Claims 13-14 and 38-49 are pending. Claim 13 is amended. Claims 1-12 and 15-37 are cancelled. Claims 38-49 are newly added. Claims 13-14 and 38-49 are under current examination.

Priority

This application claims benefit as a 371 of PCT/FR04/00354 (filed 02/17/2004). The instant application has been granted the benefit date, 17 February 2004, from the application PCT/FR04/00354.

RESPONSE TO ARGUMENTS

Claim Rejections - 35 USC § 102

The rejection of claims 13-14 under 35 USC 102(b) as anticipated over Nakamori et al. (Applied Microbial Biotechnology, 1999; 52: 179-185), is withdrawn in response to Applicant's amendment or arguments. Applicant's arguments have been fully considered are persuasive. Therefore, the examiner hereby withdraws the rejection of claims 13-14 as anticipated over Nakamori et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The examiner acknowledges the applicant's request to hold in abeyance the provisional ODP rejection of claims 13-14. However, because the substance of the rejection was not addressed and overlap between the claim sets of the two applications has not changed, the examiner hereby maintains the rejection. In fact, Application No. 10/781499 has been amended to introduce new claims which are identical to those introduced in the instant application. Therefore, the instant rejection has been altered to include rejection of the newly added claims.

Claims 13-14 and 38-49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1, 12-14 and 38-49 of copending Application No. 10/781499 (US2005/0054060). Although the conflicting claims are not identical, they are not patentably distinct from each other because the method steps of producing an evolved protein (claim 13 of instant application) require producing an evolved microorganism (as recited in claim 1 of 10/781499). The evolved microorganism of 10/781499 would produce an evolved protein. Furthermore, claims 12-13 of 10/781499 recite production and isolation of an evolved protein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

NEW GROUNDS OF REJECTION

Claim Objections

Claim 49 is objected to because of the following informalities: Claim 49 is directed to the method of claim 13, wherein the microorganism is *E. coli* **and** *C. glutamicum* (emphasis added by examiner). The instant specification does not describe a method that uses two different microorganisms, so the examiner believes the instant claim contains a grammatical error, where the instant claim should recite "or" rather than "and." In particular, the specification describes using either *E. coli* or *C. glutamicum* on page 8, lines 8-10 of the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 USC § 112, p 1 "Written Description" Requirement;* (Federal Register/Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claim 42 is directed to the method of claim 13, wherein, in step (c) a co-substrate is added to the defined medium. The examiner points out that step (c) is directed to "selecting an evolved microorganism" and not "culturing" as in step (b). The examiner was unable to find an embodiment that corresponds to claim 42. Example F, page 45, seems to add the co-substrate in step (b).

Therefore, the examiner considers this claim to be new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-14, 38-41 and 43-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richaud et al. (J. Biological Chemistry. December 25, 1993;

268(36):26827-26835) in view of Short et al. (US2005/0124010, published June 19, 2005).

Claim 13 is directed to a method for the producing an evolved protein comprising a) generating a directed genetic modification in a gene of interest in an initial microorganism to yield a modified microorganism, wherein the production or consumption of a substrate is inhibited when the modified microorganism is grown on a defined medium, wherein the ability of the modified microorganism to grow is impaired; b) culturing the modified microorganism obtained in step (a) on the defined medium allowing the modified microorganism to evolve a compensatory metabolic pathway, wherein the defined medium can contain a co-substrate promoting the evolution; c) selecting an evolved microorganism from step (b) able to grow on the defined medium, wherein at least one protein has evolved in the metabolic pathway compensating for the inhibition allowing the modified microorganism to proliferate; d) isolating the evolved protein.

The specification defines an evolved protein as “a sequence of amino acids (protein sequence) that differs in at least on amino acid from the initial protein sequence after selection” (page 4, lines 5-8). According to the specification, selection is defined as “a culture method used to select microorganisms that have evolved in such a way that a modification does not affect growth anymore” (page 3, lines 22-24). The specification does not define the phrase “compensatory metabolic pathway.” The specification also does not explicitly define the phrase “directed genetic modification.” Accordingly, the examiner will interpret these terms broadly.

Richaud et al. teach "disrupting the metC gene" (abstract) of *E. coli*, which the examiner interprets as satisfying the limitations directed to "generating a directed genetic modification in a gene of interest in an initial microorganism," as described in part a) of claim 13. Richaud et al. teach "a latent metabolite could under certain circumstances fulfill an essential need in cell chemistry, the way would be open for establishing a biosynthetic pathway *de novo*" (page 26827, col.1), which satisfies the limitations of part b) claim 13, directed to evolution of a compensatory metabolic pathway. Richaud et al. also teach "expansion of thioether biosynthesis in *Escherichia coli* generates sulfur-containing amino acids that can replace meso-diaminopimelate, the essential amino acid used for cross-linking the cell wall," and "[a]s a result, meso-lanthionine and L-allo-cystathione were produced endogenously and incorporated in the peptidoglycan, thereby enabling *E.coli* strains auxotrophic for diaminopimelate to grow in its absence" (abstract), which the examiner interprets as satisfying the limitations of part c) of claim 13 directed to "wherein at least one protein has evolved in the metabolic pathway compensating for the inhibition allowing the modified microorganism to proliferate." Richaud et al. describe this process, "techniques of metabolic engineering can be applied to evolving the chemical constitution of living cells beyond its present state" (abstract), which is similar to the broad outline of the instant invention provided by the specification. Furthermore, Richaud et al. teach "a metC mutation enhances the growth of *dap* strains exogenously supplied with L-lanthionine, meso-lanthionine, or L-allo-cystathionine as the cross-linking amino acid' and is absolutely required for growing such strains with exogenous L-cystathionine (Table VI). The broad activity of

cystathionase, which is indeed known to degrade generically L-cysteine thioethers in vitro, can thus be rationalized as fulfilling a corrective task, which adds to the biosynthetic function of the enzyme in E. coli metabolism " (page 26834, col.1, parag.1), which the examiner interprets as satisfying the limitations of part a) and b) of claim 13, directed to "wherein the production or consumption of a substrate is inhibited when the modified microorganism is grown on a defined medium, wherein the ability of the modified microorganisms to grow is impaired" and "wherein the defined medium can contain a co-substrate." Richaud et al. further indicate, [t]hese strains can thus be viewed as having undergone an evolutionary commitment to use cystein thioethers for building their cell wall. Although this commitment did not result from natural selection but was rationally set up in their genome, the fitness of the committed strains might now be improved my natural selection" (page 26834, col.2, parag.1).

The only element of claim 13 not taught by Richaud et al. is part d), directed to isolation of the evolved protein.

Claims 38-39 are directed to the method of claim 13, wherein the gene of interest (claim 38) or evolved protein (claim 39) is homologous or heterologous. The specification teaches "[t]his invention also concerns a method comprising an additional step a1) in which at least one heterologous gene coding for a heterologous protein is introduced, which heterologous gene is intended to cause the evolution of a new metabolic pathway" (page 2, lines 9-11). Richaud et al. teach "jointly overexpressing the *metB* gene coding for L-cystathionine γ-synthase and disrupting the *metC* gene"

(abstract). In this case, the disrupted *metC* gene is the homologous gene of interest and the overexpressed *metB* gene the heterologous evolved protein.

Claim 40 is directed to the method of claim 13, wherein the defined medium is substantially free of the substrate the production or consumption of which is inhibited in the modified microorganism. In the example of Richaud et al., the substrate is meso-diaminopimelate. Richaud et al. teach “thereby enabling *E.coli* strains auxotrophic for diaminopimelate to grow in its absence” (abstract). It seems that the substrate is not present in the medium of these *E.coli* strains.

Claim 41 is directed to the method of claim 13, wherein in step (b) a co-substrate is added to the defined medium. Richaud et al. teach "[g]rowth of *E. coli* mutants bearing a deletion of the diaminopimelate pathway in the presence of lysine and in the absence of diaminopimelate there provide an inescapable selection screen for the endogenous production of diaminopimelate substitutes." (bottom page 26827 bridging 26828). This seems to satisfy the limitations of claim 41.

Claim 43 is directed to the method of claim 13, wherein the protein having evolved in the compensatory pathway is encoded by a gene being homologous gene or heterologous gene. The specification teaches “[t]his invention also concerns a method comprising an additional step a1) in which at least one heterologous gene coding for a heterologous protein is introduced, which heterologous gene is intended to cause the evolution of a new metabolic pathway” (page 2, lines 9-11). Richaud et al. teach “jointly overexpressing the *metB* gene coding for L-cystathionine γ-synthase and disrupting the

metC gene" (abstract). In this case, the overexpressed *metB* gene encodes the heterologous evolved protein.

Claim 44 is directed to the method of claim 13, wherein the genetic modification comprises the directed mutation or deletion of a gene of interest or the directed modification of a promoter in the gene of interest. Richaud et al. teach "disrupting the metC gene" (abstract) of *E. coli*, which the examiner interprets as satisfying the limitations directed to "generating a directed genetic modification in a gene of interest in an initial microorganism," as described in part a) of claim 13.

Claim 45 is directed to the method of claim 13, wherein the genetic modification consists in the removal of most of the gene of interest. Richaud et al. teach "disrupting the metC gene" (abstract) of *E. coli*, which the examiner interprets as satisfying the limitations directed to "generating a directed genetic modification in a gene of interest in an initial microorganism," as described in part a) of claim 13. The type of mutation does not seem to be particularly important to the practice of the method. Any type of null mutant, whether created by a deletion, point mutation, etc would be obvious in light of the teachings of Richaud et al.

Claim 46 is directed to the method of claim 13, wherein the gene of interest is replaced with a selection marker gene. The type of mutation does not seem to be particularly important to the practice of the method. Any type of null mutant, whether created by a knockout by replacing the gene of interest with a selection marker, or by any other known means, would be obvious in light of the teachings of Richaud et al.

Claim 47 is directed to the method of claim 13, wherein the microorganism is selected among bacteria, yeasts, and fungi. Richaud et al. teach a method which uses *E. coli.*

Claim 48 is directed to the method of claim 13, wherein the microorganism is…[various microorganisms] including *Escherichia sp*. Richaud et al. teach a method which uses *Escherichia coli.*

Claim 49 is directed to the method of claim 13, wherein the microorganism is *E. coli* and *C. glutamicum.* The instant specification does not describe a method that uses two different microorganisms, so the examiner is interpreting the instant claim as reciting "or" rather than "and." In particular, the specification describes using either *E. coli* or *C. glutamicum* on page 8, lines 8-10 of the specification. Richaud et al. teach a method which uses *E. coli.*

Richaud et al. does not teach all the limitations of claim 13. The only element of claim 13 not taught by Richaud et al. is part d), directed to isolation of the evolved protein.

However, Short et al. teach "directed evolution…generating transgenic organism, such as microbe" (abstract). Short et al. further teach isolating cells which produce a desired metabolite (paragraphs 1062-1063) and also teach measuring metabolic parameters such as growth, as well as "changes in the expression of the polypeptide can be measured by any method, e.g., a one-dimensional gel electrophoresis,…western blot" (parag.1070). Short et al. teach that cystathionine synthase is an example of the gene or gene product used in their methods.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Richaud et al and Short et al. so that the evolved protein produced by the microorganisms of Richaud et al are isolated.

The person of ordinary skill in the art would have been motivated to make those modifications because Short et al. suggest measuring expression levels of the evolved protein, as an alternative or in addition to measurement such as growth on defined media.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Richaud et al. and Short et al. because each of these teachings generated evolved microorganisms and discuss the proteins which make possible the growth of the auxotrophic organisms.

Therefore the method as taught by Richaud et al. in view of Short et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SCOTT LONG/
Examiner, Art Unit 1633